

# 合成カルバゾール系化合物の抗小胞体ストレス活性に関する評価

三浦比佳理\*、高野 桂\*、北尾康子\*、日比野俐、町支臣成、  
村上里香\*\*、鈴木啓仁\*\*\*、山田昌司\*\*\*、小川 智\*、堀 修\*

*Journal of Pharmacological Sciences*, **108**, 164-171 (2008).

## A Carbazole Derivative Protects Cells Against Endoplasmic Reticulum (ER) Stress and Glutathion Depletion

Hikari Miura\*, Katsura Takano\*, Yasuko Kitao\*, Satoshi Hibino,  
Tominari Choshi, Rika Murakami\*\*, Hiroto Suzuki\*\*\*, Masashi Yamada\*\*\*,  
Satoshi Ogawa\*, and Osamu Hori\*

**ABSTRACT** : Enhanced levels of intracellular stresses such as oxidative stress and endoplasmic reticulum (ER) stress are implicated in various neuropathological conditions including brain ischemia and neurodegeneration. During a search for compounds that regulate ER stress and ER stress-induced cell death, we identified a carbazole derivative 9-(3-cyanobenzyl)-1,4-dimethylcarbazole (**16-14**) that protected against both ER stress and glutathione depletion. **16-14** suppressed tunicamycin (Tm)-induced cell death in both F9 Herp KO cells and PC12 cells, and its regulation of ER stress was associated with reduced levels of unfolded protein response (UPR) signaling. ER stress caused by overexpression of a fluorescent ER-resident protein, GFP-KDEL, KDEL. **16-14** also prevented glutathione depletion-induced cell death caused by buthionine sulfoximine (BSO), but not likely via its anti-oxidative activity. Further analysis revealed that **16-14** suppressed increases in intracellular  $\text{Ca}^{2+}$  in response to thapsigargin (Tg). These results suggest that **16-14** may protect cells against different stresses via the maintenance of intracellular  $\text{Ca}^{2+}$  homeostasis.

抄録 脳虚血や神経変成などの疾患治療薬を目的とし、小胞体ストレスおよびツニカマイシンで細胞死を惹起した小胞体ストレスを調節する化合物の探索において、カルバゾール系化合物の中で、9-(3-cyanobenzyl)-1,4-dimethylcarbazole (**16-14**) が小胞体ストレスおよびグルタチオン欠損の細胞死に対して、最も強く調節や保護作用を示すことが分かった。

\* Department of Neuroanatomy and Department of Molecular Pharmacology, Kanazawa University Graduate School of Medical Science  
金沢大学大学院医学系研究科

**\*\* Division of Research and Development, Meiji Dairies Corporation**

明治乳業株式会社

**\*\*\* Hanno Research Center, Taiho Pharmaceutical Co.**

大鵬薬品工業株式会社